Remarks

Application Status and Disposition of Claims

The Office Action considered claim 1, claims 2-4 having been cancelled and claims 5-13 having been withdrawn from consideration as directed to a non-elected invention. The withdrawn claims have been allowed to remain pending, subject to possible rejoinder.

Claim Rejections – 35 U.S.C. § 112, First Paragraph

In the Office Action, the Office maintains the rejection of claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. (Office Action at paragraph 2.) The reasons were set forth in the previous Office Actions, and are summarized as follows. The Office asserts that the claims lack full enablement because: 1) post-filing mutation association studies of the SNP recited in the present claims show a lack of unpredictability in that they show variation depending on the population studied; and 2) a large amount of experimentation would be required to practice the invention because, in view of the variability seen in relevant studies, the practitioner would be required to conduct many studies to obtain reliable correlative data. Applicants traverse this rejection.

The Office relies on the disclosures and conclusions of *Mangino*, *Sedlacek*, *Kimura*, and *Li* (all of record) to show that there was no consensus as to whether the SNP recited in the present claims was correlated with myocardial infarction (MI). Applicants disagree, and submit that the studies relied upon by the Office were either flawed in the selection of the population to study, or, in fact, support enablement for Applicants' claimed invention. For ease of reference,

Applicants will address each cited reference in the order that it was discussed in the Office Action.[1]

The Office relies on *Mangino* to teach that the SNP of the present claims is not associated with MI in Caucasians. Applicants submit that the data presented by *Mangino* cannot be relied upon for the conclusion drawn. As discussed previously by Applicants, the study, and thus conclusions, of *Mangino* are faulty and cannot be relied upon. Specifically, the association studies of *Mangino* fail to take into account sampling bias with regard to the genetically diverse population tested. It is widely understood in the art that association analyses must have adequately large sample numbers and that hierarchization of the sample (*i.e.*, sampling bias) must not be present. The sample populations studied in *Mangino* were genetically diverse, yet *Mangino* does not account for the sampling bias in the tested population. This is a significant design flaw that one of skill in the art would immediately recognize. It is further a design flaw that would cause the skilled artisan to discount the conclusions drawn by *Mangino*. Applicants respectfully submit that the teachings of *Mangino* would not be relied upon by the skilled artisan to conclude that there is no association between the 3279C->T SNP and any arteriosclerotic disease, and myocardial infarction in particular. Applicants thus submit that the Office similarly should not rely on *Mangino* for such a teaching.

The Office relies on *Sedlacek* to teach that the SNP of the present claims is not associated with MI in Caucasians, and in particular with two tested German populations. Applicants submit that the data presented by *Sedlacek* cannot be relied upon for such a conclusion. As discussed previously by Applicants, the study, and thus conclusions, of *Sedlacek* are faulty and cannot be relied upon because the association studies of *Sedlacek* fail to take into account the genetic

[1] Applicants note that the Office continues to rely on *Lucentini* and *Hegele* for the general teachings concerning mutation association studies. In response, Applicants reiterate their previous arguments as to the relevance of these publications.

diversity of the populations studied (*i.e.*, sampling bias). The sample populations studied in *Sedlacek* were genetically diverse, yet *Sedlacek* does not account for the sampling bias. This is a significant design flaw that one of skill in the art would immediately recognize. It is further a design flaw that would cause the skilled artisan to discount the conclusions drawn by *Sedlacek.* Applicants respectfully submit that the teachings of *Sedlacek* would not be relied upon by the skilled artisan to conclude that there is no association between the 3279C->T SNP and any arteriosclerotic disease, and myocardial infarction in particular. Applicants thus submit that the Office similarly should not rely on *Sedlacek* for such a teaching.

The Office continues to rely on *Kimura* to teach that there is no association of the 3279C->T SNP with myocardial infarction in the Japanese and Korean populations tested. Applicants have previously noted that *Kimura* acknowledges possible reasons why the findings showed no association between the SNP and myocardial infarction. In particular, *Kimura* acknowledges that the findings require additional studies, and that the studies are flawed because the researchers did not match the background of risk factor for MI in the patients and controls, and did not evaluate coronary atherosclerosis (affected vessels) in the controls. No less importantly, the population sizes in *Kimura* are unacceptably low. Such small sample sizes do not give reliable statistical data, and would not be relied upon by a skilled artisan to draw any conclusion about correlation of an SNP with a phenotype. As such, the skilled artisan would discount the conclusions drawn by *Kimura*. Applicants submit that the Office should similarly discount the conclusions drawn in this reference.

Finally, the Office relies on *Li* to show that there was post-filing unpredictability relating to the correlation between the SNP recited in the present claims and MI. Applicants submit that the skilled artisan would immediately recognize that the metadata compiled by *Li* is not a reliable

indicator of predictability because the metadata used by *Li* fails to account for genetic diversity among and within populations. For at least this reason, Applicants submit that one of skill in the art would discount the conclusions drawn by *Li*.

Furthermore, Applicants submit that the data presented in *Li* and relied upon by the Office is not directly relevant to the presently claimed invention. Specifically, the data presented in Figures 4 and 5 of *Li* relate to the incidence of C3279T in the publications surveyed. However, this data tells the skilled artisan nothing that is relevant to the presently claimed invention because the presently claimed invention relates to the presence of a cytosine nucleotide at the cited position, not a thymine nucleotide. That is, the conclusions of *Li* relate to a correlation between the presence of thymine at position 3279, not to the presence of cytosine at that position, as currently recited in the present claims. Because of the presence of heterozygotes in the population, any purported correlation or lack thereof based on the presence of thymine has no direct relevance to a correlation between cytosine at that position and MI. The conclusion of *Li* that the metadata analysis revealed no correlation between the C3279T SNP and MI has no bearing whatsoever on the correlation recited in present claim 1.

Furthermore, the conclusions drawn in *Li* are based on improper analysis of the data. To further illustrate this point, Applicants have tabulated the data of the references cited by *Li*, as the data was collected for analysis of cytosine at position 3279. The data is presented in Table 1, below. A comparison of this data to the data presented by *Li* shows that the data of *Li* is not the proper data to use for an analysis of the predictability of a correlation between the presence of cytosine at position 3279 and MI. Specifically, *Li* combines data for various populations into a single analysis and calculation, and concludes that there is no correlation between thymine at position 3279 and MI. But, the data, if properly tabulated, instead show that there is a

statistically significant correlation between cytosine at position 3279 and MI. The statistical significance is presented below as Table 2, as the data exist when properly calculated. The metadata analysis of all populations shows P=0.0039 (in comparison of allele frequency) and P=0.0014 (TT vs others; protective), which achieves statistical significance. As such, the conclusion of *Li* is wrong. For at least this reason, Applicants submit that one of skill in the art would discount the conclusion drawn by *Li* as it relates to predictability of studies relating to such a correlation.

Table 1:

Study	No	Case-count				Control-Count			
		CC	CT	TT	Total	CC	CT	TT	Total
Mangino	1	109	382	255	746	115	324	259	698
Asselbergs	2	332	493	189	1014	668	969	402	2039
Koch	3	652	1795	1210	3657	219	574	418	1211
Sedlacek1 (first population)	4	447	568	183	1198	382	503	168	1053
Sedlacek2 (second population)	5	227	279	97	603	488	684	251	1423
Panoulas	6	10	30	25	65	53	143	125	321
Kimura1 (Japanese)	7	220	231	68	519	487	464	112	1063
Kimura2 (Korean)	8	226	193	29	448	352	292	55	699
Ozaki	9	1077	1014	211	2302	856	903	279	2038
					10552				10545

Table 2:

SNP	N	P	OR	Q	I
rs7291467 allele frequency	9	0.003861	1.062	0.0166	57.21
rs7291467 CC vs. others	9	0.1096	1.0523	0.1308	35.92
rs7291467 TT vs others	9	0.001442	0.8864	0.0189	56.35

N: number of valid studies for this SNP

P: fixed-effects meta-analysis p-value
OR: fixed-effects OR estimate
Q: p-value for Cochrane's Q statistic
I: I^2 heterogeneity Index (0-100)

In fact, when the data relied upon by *Li* are analyzed properly, a correlation for Caucasians is shown. Specifically, meta-analysis of Caucasian populations studied with respect to the protective effect of the TT homozygote condition clearly show a protective tendency. Such a meta-analysis of the data presented in *Li* is presented below in Table 3. As shown in the Table, the TT vs others shows P=0.074 and an odds ratio of 0.93. These values imply that significance might arise if the number of samples increases.

Table 3:

SNP	N	P	OR	Q	I
rs7291467 allele frequency	6	0.1624	1.0361	0.954	0
rs7291467 CC vs. others	6	0.6647	1.0184	0.6695	0
rs7291467 TT vs others	6	0.07397	0.9258	0.9951	0

N: number of valid studies for this SNP

P: fixed-effects meta-analysis p-value
OR: fixed-effects OR estimate
Q: p-value for Cochrane's Q statistic
I: I^2 heterogeneity Index (0-100)

Applicants respectfully submit that the pre- and post-filing art supports the assertion that the present specification enables the present invention, outweighing the support offered by the Office. Applicants submit that in balancing the evidence of both sides, the weight supports that the specification fully enables the claimed invention. Therefore, Applicants respectfully request the withdrawal of the 35 U.S.C. § 112, first paragraph rejection with regard to claim 1.

Conclusion

In view of the foregoing, Applicants respectfully request that the Office withdraw the remaining rejection of record, rejoin the withdrawn claims, and allow this application to pass to issue in due course. If the Office believes that anything further is necessary to place this application in condition for allowance, Applicants request that the Office contact their undersigned representative at the telephone number listed below.

Authorization is hereby provided to charge any fee necessary to maintain the pendency of the application, including any required extension of time fee, to Deposit Account No. 19-0089.

Respectfully Submitted,
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